OPIC
Office de la propriété intellectuelle du Canada

CIPO
Canadian Intellectual Property Office

Ottawa Hull K1A 0C9

(21) (A1) 2,151,443
(22) 1995/06/09
(43) 1996/01/28

(51) Int.Cl.[6] C07D 403/10; A61K 31/415

(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Cycloheptimidazole Derivatives, Method of Manufacturing the Same and Therapeutic Agents Containing These Compounds

(72) Tomiyama, Tsuyoshi - Japan ;
Tomiyama, Akira - Japan ;
Yanagisawa, Takashi - Japan ;
Wakabayashi, Shuichi - Japan ;

(71) Kotobuki Seiyaku Co., Ltd. - Japan ;

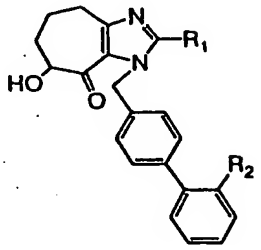
(30) (JP) 175234/94 1994/07/27

(57) 5 Claims

ABSTRACT

2151443

Cycloheptimidazole derivatives of following general formula,



(1)

(Wherein R1 is represents a lower alkyl, R2 represents tetrazole)
method of manufacturing the same and therapeutic agents containing these compounds.

New cycloheptimidazole derivatives of the present invention have angiotensin II receptor antagonistic activities and are therefore useful as treatment agent for hypertension or congestive heart failure or intraocular pressure lowering agent are proposed.

SPECIFICATION

TITLE OF THE INVENTION

Cycloheptimidazole Derivatives, Method of Manufacturing the Same and Therapeutic Agents Containning These Compounds.

BACKGROUND OF THE INVENTION

1. FIELD OF THE INVENTION

This invention relates to a novel cycloheptimidazole derivative, a production method thereof, and a treatment agent for hypertension, congestive heart failure and intraocular pressure lowering agents containing the cycloheptimidazoles.

2. DESCRIPTION OF THE PRIOR ART

Many therapeutic agents have been developed as antihypertensive agents, anticongestive heart failure agents and intraocular pressure lowering agents. One approach is to use angiotensin converting enzyme (ACE) inhibitors. In the renin-angiotensin system (RAS), angiotensinogen is hydrolyzed to angiotensin I (AI) by the renin, and AI is converted to the final product, angiotensin II (AII), which have a strong vasoconstrictive action. It has been well known that AII is related to cause hypertension and congestive heart failure. These ACE inhibitors are currently used to inhibit the formation of AII. Another approach is to block the action of AII at the AII receptor level. Recently, as the AII receptor antagonists, we are proposed the cycloheptimidazole derivatives (Japanese patent publication Laid-open 5-320139 (1993)) which provide a treatment agent for hypertension and congestive heart failure.

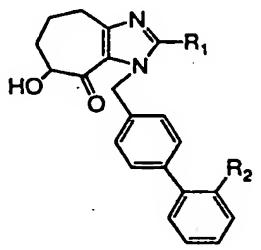
3. OBJECT OF THE INVENTION

A primary object of the present invention is to find a new cycloheptimidazole derivatives having an orally active angiotensin II receptor antagonist and provide a treatment agent for hypertension and congestive heart failure or an intraocular pressure lowering agent and a production method thereof.

SUMMARY OF THE INVENTION

The inventors have conducted intensive studies on the metabolism of cycloheptimidazole derivatives (Japanese patent publication Laid-open 5-320139 (1993)), and found that there compounds in metabolism of cycloheptimidazole derivatives which have angiotensin II receptor antagonist effect, achieving the present invention.

In accordance with the present invention, there is provided a new cycloheptimidazole derivative compound of formula (1) or its salt capable of being used for medical treatment.



(1)

(Wherein R1 represents a lower alkyl (e.g. C1 to C5 alkyl) group; R2 represents tetrazole group.)

The compounds related on the general formula (1) (cycloheptimidazole derivatives) are exemplified as follows. to

(1) 5 - [2 - (4 - (2 - Methyl - 7 - hydroxy - 8 - oxo - 4, 5, 6, 7 - tetrahydro - 1 (4H) - cycloheptimidazolyl) methylbiphenyl)] tetrazole (Compound 1)

(2) 5 - [2 - (4 - (2 - Ethyl - 7 - hydroxy - 8 - oxo - 4, 5, 6, 7 - tetrahydro - 1 (4H) - cycloheptimidazolyl) methylbiphenyl)] tetrazole (Compound 2)

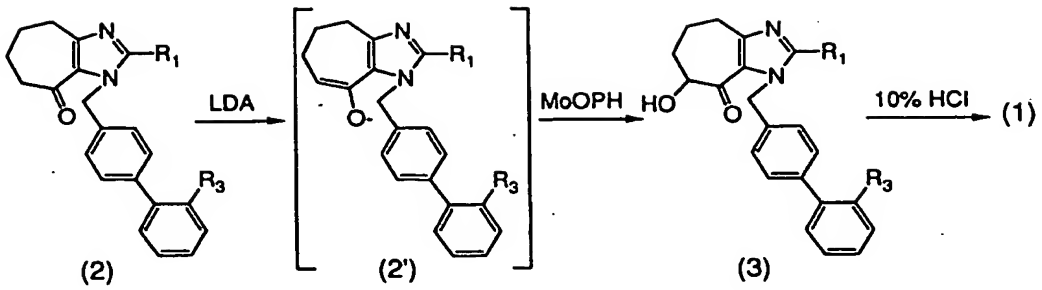
(3) 5 - [2 - (4 - (2 - Propyl - 7 - hydroxy - 8 - oxo - 4, 5, 6, 7 - tetrahydro - 1 (4H) - cycloheptimidazolyl) methylbiphenyl)] tetrazole (Compound 3)

(4) 5 - [2 - (4 - (2 - Butyl - 7 - hydroxy - 8 - oxo - 4, 5, 6, 7 - tetrahydro - 1 (4H) - cycloheptimidazolyl) methylbiphenyl)] tetrazole (Compound 4)

(5) 5 - [2 - (4 - (2 - Pentyl - 7 - hydroxy - 8 - oxo - 4, 5, 6, 7 - tetrahydro - 1 (4H) - cycloheptimidazolyl) methylbiphenyl)] tetrazole (Compound 5)

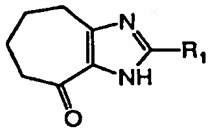
The compounds related to the general formula (1) possess a potent angiotensin II receptor antagonist from pharmacological experiment as later explain. For example, the pharmacological effect and its duration of 5 - [2 - (4 - (2 - propyl - 7 - hydroxy - 8 - oxo - 4, 5, 6, 7 - tetrahydro - 1 (4H) - cycloheptimidazolyl) methylbiphenyl)] tetrazole, orally administered, were equipotent as those of 5 - [2 - (4 - (2 - propyl - 8 - oxo - 4, 5, 6, 7 - tetrahydro - 1 (4H) - cycloheptimidazole).

The compounds (1) of the invention can be administered orally in the form of tablets, capsules, granules and syrups and also can be administered not orally such as direct administration to rectal and in the form of injections. An effective dosage of the compound is from 10 to 1000mg once to several times a day for adults, though it may be adjusted depending on age and symptoms. The invention compound of general formula (1) can be prepared by the following procedure.



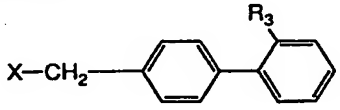
(Wherein R1, R2, R3 are the same as mentioned above).

Cycloheptimidazole derivatives (2) are reacted with LDA (lithium diisopropylamine) or K-O-t-Bu (tert-butoxy potassium) to give the compound (2'), and then (2') reacted with Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) (MoOPH) (J. Org. Chem., 43, 188 (1978)), or [(EtO)3P] triethylphosphite (J. Org. Chem., 33, 3294 (1968)) to give the compound (3). As a solvent used in this reaction, ethylether (Et2O) or tetrahydrofuran (THF). The reaction compound (3) is detritylated with 10% HCl to give the inventional compounds of cycloheptimidazole derivatives (1). The compound of cycloheptimidazole derivatives (2) which is described above, can be obtained according to the method of Japanese patent publication Laid-open 5-320139 (1993). For example, the following general formula (4)

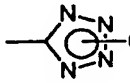


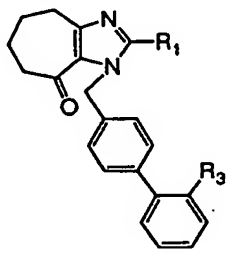
(4)

(Wherein R1 represents a lower alkyl)
react with general formula (5)



(5)

(Wherein R3 is  C(Ph)3 (ph represents phenyl) X represents bromine.) to give the compound of general formula (2)



(2)

(Wherein R_1 and R_3 are the same as mentioned above).

PHARMACOLOGICAL EXPERIMENT

[Angiotensin II receptor antagonist activity]

Angiotensin II receptor antagonistic activity experiments are carried out according to P. C. Wong et al. (Hypertension, 15, 823 (1990)). Thoracic rabbit aorta is isolated, contracted by angiotensin II. The inhibition of contraction by 5 - [2 - (4 - (2 - ethyl - 7 - hydroxy - 8 - oxo - 4, 5, 6, 7 - tetrahydro - 1 (4H) - cycloheptimidazolyl) methylbiphenyl)] tetrazole (compound 2) and 5 - [2 - (4 - (2 - propyl - 7 - hydroxy - 8 - oxo - 4, 5, 6, 7 - tetrahydro - 1 (4H) - cycloheptimidazolyl) methylbiphenyl)] tetrazole (compound 3) is expressed as pA_2 from dose-response curve according to the method of Schild (Brit. J. Pharmacol., 14, 48 (1959)). The result was shown as following, the compound (2) was 9.26 (pA_2) and the compound (3) was 9.32 (pA_2).

DESCRIPTION OF PREFERRED EMBODIMENTS

This investigation was not limited the following pharmacological experiment and preparing experiment.

Example 1.

5 - [2 - (4 - (2 - Propyl - 7 - hydroxy - 8 - oxo - 4, 5, 6, 7 - tetrahydro - 1 (4H) - cycloheptimidazolyl) methylbiphenyl)] tetrazole.

(i) 1 - Trityl - 5 - [2 - (4 - (2 - propyl - 7 - hydroxy - 8 - oxo - 4, 5, 6, 7 - tetrahydro - 1 (4H) - cycloheptimidazolyl) methylbiphenyl)] tetrazole.

To a solution of diisopropylamine (0.13ml) in THF (2ml) was added n-BuLi (0.96ml) at -78℃, and the mixture was stirred for 15min. Then 1 - Trityl - 5 - [2 - (4 - (2 - propyl - 8 - oxo - 4, 5, 6, 7 - tetrahydro - 1 (4H) - cycloheptimidazolyl) methylbiphenyl)] tetrazole (690mg) in 5ml of THF was dropwised. After 15min stirring at -78℃, the mixture warmed at -25℃ and then MoOPH (J. Org. Chem., 43, 2, (1978)) (650mg) was added. The reaction mixture was stirring at -25℃ for 30min, and quenched with aq Na_2SO_3. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and then brine and dried (Na_2SO_4), filtered, and concentrated under vacuum. The resulting product was purified by silica gel columnchromatography. Elution was carried out with ethyl acetate/n-hexane (1/1). The object compound was obtained as a white solid (380mg) : mp : 165～167℃, MS (m/e) : (M^+ -54) = 630, 243 (BP)

IR (KBr, cm^{-1}) : 3450, 1630, 744, 699

^{1}H-NMR ($CDCl_3$, ppm) δ : 0.90 (3H, t, $-CH_2CH_2\underline{CH_3}$), 1.10～2.80 (10H, m, $-CH_2\underline{CH_2}CH_3$ +Cyclo), 3.00 (2H, t, $-\underline{CH_2}CH_2CH_3$), 4.00～4.35 (1H, m, $-\underline{CH}OH$), 4.60 (1H, S, OH), 5.45

(2H, q, -C<u>H</u>2-C6H5), 6.60～7.90 (23H, m, aromatic).

(ii) 5 - [2 - (4 - (2 - Propyl - 7 - hydroxy - 8 - oxo - 4, 5, 6, 7 - tetrahydro - 1 (4H) - cycloheptimidazolyl) methylbiphenyl)] tetrazole.

The compound (150mg) which was prepared by method (i) of reference 1 was dissolved in THF (3ml). 10% HCl (1.5ml) was added and the mixture was stirred at room temperature for 6hrs. After the reaction mixture was concentrated under vacuum, treated with 20% NaOH to adjust the pH4. The reaction mixture was extracted with chloroform, and the chloroform layer was washed with water and dried (Na_2SO_4), filtered and concentrated under vacuum. The resulting product was purified by silica gel columnchromatography. Elution was carried out with chloroform/methanol (3/1). The object compound was obtained as a white solid (60mg). mp = 74～76℃

MS (m/e) : M^+ = 442, 413, 207, 178 (BP)

IR (KBr, cm^{-1}) : 2926, 1638, 1467, 1377

^{1}H-NMR ($CDCl_3$, ppm) δ : 0.90 (3H, t, -$CH_2CH_2C\underline{H}_3$), 1.10～2.80 (10H, m, -$C\underline{H}_2C\underline{H}_2CH_3$ +Cyclo), 4.00～4.35 (2H, m, -O<u>H</u>+-C<u>H</u>OH), 5.45 (2H, q, -C<u>H</u>2-C6H5), 6.60～7.90 (8H, m, aromatic).

1 - Trityl - 5 - [2 - (4 - (2 - propyl - 8 - oxo - 4, 5, 6, 7 - tetrahydro - 1 (4H) - cycloheptimidazolyl) methylbiphenyl)] tetrazole which was used Example 1, was prepared by method of Japanese patent publication Laid-open 5-320139 (1993).

To a solution of sodium hydroxide (1.0g) in water (2ml), 1, 4 - dioxane (30ml) and propylamidine hydrochloride (1.0g) were added and followed by addition of tosyltropolone (2.7g) dropwise. The separated reaction mixture was stirred at room temperature for 6hrs and poured into ice-water. The aqueous solution was treated with 10% HCl dropwise to adjust the pH5.0. The resulting precipitate was collected by filtration, and was recrystallized with ethyl acetate. 2 - Propyl - 8 - oxo - 1 - cycloheptimidazole (0.5g) was obtained.

2 - Propyl - 8 - oxo - 1 - cycloheptimidazole (0.5g) was added into toluene (20ml). 50% NaOH aqueous solution (1.5ml) was added and the mixture was stirred at room temperature for 30min. 1 - Trityl - 5 - [2 - (4 - bromomethylbiphenyl)] tetrazole (1.91g) and tetrabutylammonium hydrogensulfate (53mg) were then added and the reaction mixture was stirred at 40℃ for 24hrs. The solution was filtered, and the concentrated under vacuum. The resulting oil was purified by column chromatography on 80g of silica gel and eluted with n-hexane - ethyl acetate (1 : 1). 1 - Trityl - 5 - [2 - (4 - (2 - propyl - 8 - oxo - 1 - cycloheptimidazolyl) methylbiphenyl)] tetrazole was obtained as a white solid (0.4g).

MS (m/e) : M^+ -54 = 614, 218 (BP)

Example 2.

5 - [2 - (4 - (2 - Ethyl - 7 - hydroxy - 8 - oxo - 4, 5, 6, 7 - tetrahydro - 1 (4H) - cycloheptimidazolyl) methylbiphenyl)] tetrazole.

(i) 1 - Trityl - 5 - [2 - (4 - (2 - ethyl - 7 - hydroxy - 8 - oxo - 4, 5, 6, 7 - tetrahydro - 1 (4H) - cycloheptimidazolyl) methylbiphenyl)] tetrazole.

To a solution of diisopropylamine (0.13ml) in THF (2ml) was added n-BuLi (0.96ml) at -78℃, and the solution was stirred for 15min. Then 1 - Trityl - 5 - [2 - (4 - (2 - ethyl - 8 - oxo - 4, 5, 6, 7 - tetrahydro - 1 (4H) - cycloheptimidazolyl) methylbiphenyl)] tetrazole (950mg) in 5ml of THF 5ml was added dropwise. After 15min stirred at -78℃, the mixture warmed at -25℃ and then MoOPH (J. Org. Chem., 43, 2, (1978)) (650mg) was added. The reaction mixture was stirring at -25℃ for 30min, and quenched with aq Na_2SO_3. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and then brine and dried (Na_2SO_4), filtered, and concentrated under vacuum. The resulting product was purified by silica gel columnchromatography. Elution was carried out with ethyl acetate/n-hexane (1/1). The object compound was obtained as a white solid (310mg) : mp : 112～115℃, MS (m/e) : M^+ -56 = 614, 165 (BP).

IR (KBr, cm^{-1}) : 3424, 1635, 1467, 747.

(ii) 5 - [2 - (4 - (2 - Ethyl - 7 - hydroxy - 8 - oxo - 4, 5, 6, 7 - tetrahydro - 1 (4H) - cycloheptimidazolyl) methylbiphenyl)] tetrazole.

The compound (300mg) which was prepared by method (i) of reference 2 was dissolved in THF (4ml). 10% HCl (3ml) was added and the mixture was stirred at room temperature for 8hrs. After the reaction mixture was concentrated under vacuum, treated with 10% NaOH to adjust the pH4. The reaction mixture extracted with chloroform (20ml×3), and chloroform layer was washed with water and dried (Na_2SO_4), filtered and concentrated under vacuum. The resulting product was purified by silica gel columnchromatography. Elution was carried out with chloroform/methanol (25/1). The object compound was obtained as a white solid (180mg). mp = 94～95℃

MS (m/e) : M^+ = 428, 399, 207, 178 (BP).

IR (KBr, cm^{-1}) : 3418, 2920, 1641, 1377

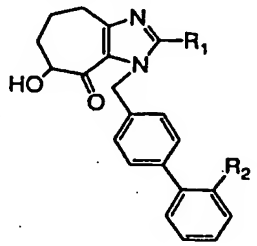
^{1}H-NMR ($CDCl_3$, ppm) δ : 1.14 (3H, t, -$CH_2\underline{CH_3}$), 1.59～2.80 (2H, m, Cyclo), 1.85～2.30 (2H, m, Cyclo), 2.51 (2H, q, -$\underline{CH_2}CH_3$), 2.55～2.65 (2H, m, Cyclo), 4.18～4.21 (2H, m, -$\underline{OH}$ +-$\underline{CH}$OH), 5.55 (2H, q, -$\underline{CH_2}C_6H_4$), 6.80～8.00 (8H, m, aromatic).

EFFECT OF INVENTION

New cycloheptimidazole derivatives of the present invention have angiotensin II receptor antagonistic activities and are therefore useful as treatment agents for hypertension or congestive heat failure or intraocular pressure lowering agents.

CLAIMS

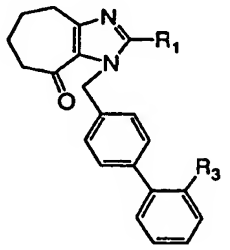
1. A compound of general formula (1) or a salt thereof



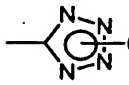
(1)

(Wherein R1 represents a lower alkyl ; R2 represents tetrazole.)

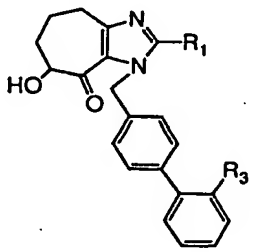
2. Following general formula (2)



(2)

(Wherein R1 represents a lower alkyl ; R3 represents  (Ph respects phenyl))

react with lithium diisopropylamine or tert-butoxypotassium and then oxodiperoxymolybdenum (pyridine)(hexamethylphosphoric triamide) or triethyl phosphite to give the following general formula (3),



(3)

(Wherein R1 and R3 are the same as mentioned above) and then said compound is detritylating to

give the compound of general formula (1).

3. A treatment agent for hypertension comprising a compound as claimed in claim 1, as an active ingredient.

4. A treatment agent for congestive heart failure comprising a compound as claimed in claim 1, an active ingredient.

5. An intraocular pressure lowering agent comprising a compound as claimed in claim 1, as active ingredient.